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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,314	04/11/2006	Mark Noble	176/61404(6-1058)	8649

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EXAMINER	
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ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,314	NOBLE ET AL.	
	Examiner	Art Unit	
	GIGI HUANG	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *13-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/30/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II in the reply filed on April 1, 2008 is acknowledged. The traversal is on the ground that claims 13 and 15 recite the use of a composition according to claims 1 and 12 of Group I. This is not found persuasive because the claims are subject to a lack of unity which has been addressed in the previous restriction.

The requirement is still deemed proper and is therefore made FINAL.

Status of Application

2. Applicant has elected Group II in response to restriction requirement for the examination.

Due to restriction, based on election of Group II, claims 1-12 and 24-37 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Applicant's election of caspase 3 inhibitors and non-caspase inhibiting alkylating anti-cancer agents has been broadened.

Claims 13-23 are present for examination at this time.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 13-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a "caspase inhibitor" and an inhibitor that is a "pan caspase inhibitor", an inhibitor "specific for caspase-3, caspase-8, or caspase -9", and wherein the caspase inhibitor "inhibits the production of a caspase" or "inhibits the activation of a caspase" or inhibits a signaling pathway of a caspase". The description is inadequate to one of skill in the art to distinguish what the inventors were in possession of at the time of filing.

First, claims and description define the caspase inhibitors and inhibitors specific for a particular caspase, by what it *does* and not *what it is*. Second, it does not describe adequately the degree of inhibition or specificity for the caspase of type of caspase that would fulfill the description.

As addressed in the specification (Page 11 lines 1-3) c-DEVD-DHO inhibits caspase-3 preferentially but is not solely specific for caspase-3. As there is no adequate description as to the degree of preferential attachment for caspase-3 to be considered specific for the caspase, the fact pattern indicates that the artisan was not in possession of the claimed method of use. Additionally, Petak et al. (BCNU….) teaches that BCNU is both a caspase-mediated inhibitor and an anticancer agent. The specification however, addresses BCNU (carmustine) as an anti-cancer agent, not as a caspase inhibitor, which as taught by Petak, has the capacity to inhibit drug-induced apoptosis from etopside at certain doses.

Specifically, BCNU is addressed as a species of alkylating agent to the broader grouping *of non-caspase inhibiting anti-cancer agents* which conflicts with the teachings of Petak where *BCNU is caspase-inhibiting*. The specification does not adequately disclose what is encompassed by the term and the caspase inhibitors specifically recited in the specification are protein/peptide inhibitors and BCNU is a mustard derivative/alkylating agent. The disclosure does not clearly describe what the inventors were in possession of at the time of filing. As a result, the fact pattern indicates that the artisan was not in possession of the claimed method of use.

As indicated by Okun et al. (Screening for Caspase-3 Inhibitors:...), caspases inhibitors, particularly caspase-3 inhibitors are an ongoing endeavor for pharmaceutical companies in a search for effective drugs. Okun teaches that screening methods were utilized to find caspase-3 inhibitors from their 650000 compound collection, where about 15000 potential inhibitors were subject to the screening against caspase-3 resulting in one particular compound (CD-001-0011)that was synthesized and tested for a class of double electrophillic warhead small-molecule inhibitors. Okun teaches that the mechanism for susceptitibility of the caspase-3 is unclear and subject to speculation (Discussion). As new caspase inhibitors are still being explored and the exact mechanisms for inhibitors are unclear, the fact pattern indicates that the artisan was not in possession of the claimed method of use.

5. Claims 13-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a method treating cancer with a caspase inhibitor or a combination of a caspase inhibitor and a non-caspase inhibitor anti-cancer agent. Thus, the claims taken together with the specification imply that every cancer can be treated with either a caspase inhibitor or a combination of a caspase inhibitor and a non-caspase inhibitor anti-cancer agent.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The state of the prior art addresses the wide unpredictability of caspase inhibitors which is highly variable to the specific inhibitor (e.g. BCNU verses Z-VAD.FMK), the amount used, the specific combinations of components particularly with which anti-

cancer agent, the cell line, and the type of cancer can result in substantially different results.

Slee et al. (Benzyloxycarbonyl-Val-Ala-Asp…) teaches the use of Z-VAD.FMK which inhibits apoptosis (cell death) by inhibiting the processing of CPP32 (pro-caspase-3) to its active form. Slee also teaches the Z-VAD.FMK was effective in inhibiting apoptosis in THP.1 cell, but Ac-DEVD-CHO and Ac-YVAD-CHO were not effective in inhibiting apoptosis, despite the fact that Ac-DEVD-CHO is an inhibitor of caspase-3.

However, Kim et al. teaches that Ac-DEVD-CHO attenuated indomethacin-induced DNA fragmentation (apoptosis) in colon cancer cells. Wherein Ac-DEVD-CHO was not effective with THP.1 cells and cycloheximide, it was with indomethacin and colon cancer cells.

Petak et al. teaches that BCNU is a caspase-mediated inhibitor and an anticancer agent. Petak teaches that BCNU is bifunctional and has the capacity to inhibit drug-induced apoptosis from etopside at certain noncytotoxic doses (12-50um). The effects of inhibition were dependent on the dose of BCNU. BCNU is an alkylating nitrosourea derivative (mustard derivative). As a result, Petak teaches that the dose of amount as well as the specific inhibitor can directly affect the role and inhibition of the agent. Petak also teaches that the fact a cytostatic agent in a dose that is noncytotoxic can eliminate or reduce the biological activity of another drug used in combination therapy can influence the clinical response.

Koken et al. (WO 00/07616- it is noted that U.S. Pat. No. 7217413 will be used as the translation and the references are to the U.S. Pat.) teaches that inhibitors of caspases, particularly zVAD (N-benzyloxycarbonyl-valyl-alanyl-aspartyl-fluoromethylketone) are involved in the apoptosis process and that studies had shown that zVAD prevented or greatly inhibited cell death (apoptosis) . However, Koken et al. taught that zVAD did not inhibit apoptosis induced by interferons (anti-cancer agent-see Horrobin), nut contrary to expectation accelerated the apoptosis (Abstract, Col. 1 lines 1-8 and 44-Col 2 line 22, Claim 1-8).

Thereby, not all caspase inhibitors are effective in killing cancer cells, inhibiting the growth of cancer cells, and thereby treating cancer. Variables such as the particular caspase inhibitor, not just the type of caspase inhibitor (e.g. Ac-DEVD-CHO, not generally caspase-3 inhibitors, see all references above), whether in combination and what specifically it is combination with (Slee, Kim, Koken), the type of cancer (Slee, Kim), and the amount (Petak) will directly affect the outcome.

Thereby, due to the high unpredictability of the art and the wide range of possible effects that are divergent dependent of the factors addressed above, the generic use of a caspase inhibitor or a combination of a caspase inhibitor and a non-caspase inhibitor anti-cancer agent would not be enabled for treating all cancers.

(5) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has only provided guidance for combining BCNU with caspase inhibitors for killing tumor cells in the examples on pages 35-36 and the description of the drawing of figures 1-7 on pages 2-4.

However, the specification does not provide any disclosure as to which specific inhibitors were utilized in the examples which as addressed above are critical to the outcome of treating cancer. For example, which specific pan caspase inhibitor verses the subgenus of pan caspase inhibitors.

The specification does not provide what the amounts of BCNU are utilized in each example represented in the figures. As addressed above by Petak, the amount of BCNU is critical to the outcome of treatment. It also goes to the role of BCNU as if it is within the ranges of non-cytotoxic doses, it is acting as a caspase inhibitor. It is also a question as to how to use BCNU as disclosed as a non-caspase inhibitor anti-cancer agent particularly an alkylating agent, when it is known in the art to possess caspase inhibition properties.

The specification utilizes 1789 glioblastoma, UT-9 and 12 astrocytoma, and SW480 colon cancer cell lines in the examples which as addressed above are not representative of all cancers ad the type of cancer cell line and the agents used will yield various results.

The lack of disclosure does not allow one of skill in the art duplicate the examples nor to make and use the invention.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to the enablement for the methods of treatment, the lack of disclosure and guidance in the specification, and the high unpredictability in the art as evidenced therein, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Claim Rejections - 35 USC § 102

The claims are so broad as to read upon the following pieces of art:

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 13-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Koken et al. (WO 00/07616).

It is noted that U.S. Pat. No. 7217413 will be used as the translation and the references are to the U.S. Pat.

Koken et al. teaches that inhibitors of caspases are involved in the apoptosis process. Koken also teaches that certain combinations of caspase inhibitors and other agents including anti-cancer agents can result in improved apoptosis. An example is zVAD (N-benzyloxycarbonyl-valyl-alanyl-aspartyl-fluoromethylketone) where previous studies had shown that zVAD prevented or greatly inhibited cell death (apoptosis) . However, Koken et al. taught that zVAD did not inhibit apoptosis induced by interferons (anti-cancer agent-see Horrobin), but contrary to expectation accelerated the apoptosis.

This was true to other inhibitors such as DEVD (Abstract, Col. 1 lines 1-8 and 44-Col 2 line 22, Col. 3 lines 1- Col. 4 line 55, Col. 9 line 30-col. 10 line 25, Claim 1-8).

All the critical elements are taught by the cited reference and thus the claims are anticipated.

8. Claims 13-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Weber et al. (WO 01/27140).

Weber et al. teaches the use of caspase inhibitors for treating non-cancer cell death during chemotherapy and radiation therapy their related side effects. A number of caspase inhibitors are addressed including Cbz-Val-Asp-CH2F and Cbz-Val-Asp(OMe)-CH2F (caspase-3 selective) and zVAD, Weber teaches methods and modes of administration with pharmaceutical carriers, general dosages, and that the inhibitors can be sequentially, concurrently, and combined with chemotherapeutic agents such as cisplatin (Abstract, Page 11, line 15- Page 20 line 5, Page 20 line 7-Page 27 line 15).

All the critical elements are taught by the cited reference and thus the claims are anticipated.

Conclusion

9. Claims 13-23 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GIGI HUANG whose telephone number is (571)272-9073. The examiner can normally be reached on Monday-Thursday 8:30AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fredrick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GH
/Zohreh A Fay/
Primary Examiner, Art Unit 1612